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Systematic Review: Non A-E, seronegative or indeterminate hepatitis; what is this deadly disease?

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SUMMARY

Background

A significant proportion of cases of acute liver failure (ALF) do not have an identifiable cause; so called "non A-E", "non-A, non B, non C", "seronegative" or "indeterminate" hepatitis. However, this entity is clinically not well described.

Aim

To collate the known incidence and outcomes in indeterminate hepatitis. This systematic review sought to identify potential aetiologies that ought to be considered, and identify likely future objectives in classification and treatment strategies for indeterminate hepatitis.

Methods

Literature review to determine aetiological factors, prevalence and outcomes relating to indeterminate hepatitis.

Results

There is significant heterogeneity within the reported cases of indeterminate hepatitis in the literature. Some of the potential infective aetiologies which are reviewed here include; parvovirus B19 (PVB19), herpes simplex virus (HSV), Toga-Like Virus and the Annelloviridae (including SEN-V). Interestingly, this condition predominately affects middle aged women, with subacute progression of the liver failure. In addition, the prognosis of indeterminate hepatitis is poor, with reduced spontaneous survival compared with other causes of acute liver failure and increased need for emergency liver transplantation.

Conclusions

Whilst various pathological processes have been implicated in the development of indeterminate hepatitis, the specific cause remains elusive. There is an urgent need for general consensus on a specific definition and exclusion of confounding aetiologies with coordinated multicentre investigation of this rare condition to identify aetiology and develop therapies to reduce the significant mortality and need for emergency liver transplantation associated with this condition.

Introduction

Acute liver failure (ALF) is a rare and life-threatening condition occurring in patients without pre-existing liver disease. The clinical presentation may be rapidly progressive, or insidious with evidence of jaundice, coagulopathy and deranged liver enzymes. The development of clinically apparent hepatic encephalopathy differentiates those patients with severe acute liver injury (ALI) from patients with ALF[1]. Acute liver failure is associated with significant morbidity and mortality[1]. The clinical course and outcome depends upon the underlying aetiology, age of the patient, the period of time over which the disease develops, the extent of liver damage (which are all interrelated) and early institution of supportive care. [1]

The most common cause of ALF in the United Kingdom, USA and some parts of Europe is paracetamol (acetaminophen) overdose, which may be taken with suicidal intent or follow accidental consumption of excess amounts over time. Elsewhere, viral hepatitis is the most common aetiological agent. However, a significant proportion of acute liver failure cases do not have an identifiable cause; so called non A-E, seronegative or indeterminate hepatitis. Several studies have proposed the existence of hepatotrophic agents beyond those currently recognised, and others have implicated the role of hepatotoxic drugs in leading to this clinical syndrome. Previously, GB Virus C [2], hepatitis G Virus[3] and TT Virus (TTV)[4] have all been suggested as pathogenic agents, however true causation has never been substantiated[6-8]. In this review, we discuss the potential aetiological agents, clinical manifestations, treatments and clinical outcomes in non A-E, seronegative or indeterminate ALF, identifying significant gaps in current understanding of many areas of this rare condition with the aim to facilitate future studies.

Methods

This review was conducted according to PRISMA[5] statement guidelines. MEDLINE (OvidSP), PubMed, EASL (European Association for the Study of Liver) and AASLD (American Association for the Study of Liver Diseases) archives were searched for studies in acute or fulminant, hepatic or liver failure using the terms "non-A non-B" "non-A, non-B, non-C", "seronegative hepatitis", "non A-E" and "indeterminate" hepatic or liver failure. This was performed electronically to include all English language publications from 1970. The searches were limited to patients over 18 years of age. One investigator (PNB) performed an initial screen of the all relevant titles, to exclude duplicates and non-relevant articles. The search was then subsequently repeated by two investigators (PNB, MD) whereby each abstract was reviewed and relevant articles selected (Figure 1).

Nomenclature

There is widespread variability in the nomenclature used both in clinical practice and research studies to describe causes of acute liver failure not identified by standard diagnostic tests. Historically this disease entity was labelled non-A, non-B hepatitis, and as new viruses were identified non A-E hepatitis became the preferred terminology (Figure 2). This nomenclature suggests the aetiological agent for this condition is an as yet unidentified hepatotropic virus. More recently, the term 'seronegative hepatitis' has also been used. This terminology recognises the possibility of uncharacterised autoimmune or immune mediated liver injury. Latterly 'indeterminate hepatitis' has been favoured when the cause of ALF cannot be identified, perhaps covering all potential pathogenic mechanisms of liver injury. Therefore 'indeterminate hepatitis' will be the preferred term throughout this review.

O'Grady and colleagues[6] proposed modification of the definition for acute liver failure based on the time between jaundice and the development of hepatic encephalopathy: "hyperacute liver failure" occurs when encephalopathy develops within 7 days of the onset of jaundice, 'acute liver failure" when

encephalopathy develops within 8-28 days from jaundice and 'subacute liver failure" pertains to individuals with a more insidious onset of encephalopathy, developing within 5-12 weeks of the onset of jaundice. Hyperacute cases of liver failure are most commonly caused by paracetamol hepatotoxicity; is more often complicated by the development of cerebral oedema and paradoxically have the best outcomes. In contrast, indeterminate hepatitis commonly causes subacute liver failure, which can be difficult to differentiate clinically from decompensated liver cirrhosis or acute on chronic liver failure, requiring the physician to have a high degree of clinical suspicion. Such cases have poor spontaneous survival rates and are major indications for emergency liver transplantation. As previously indicated encephalopathy differentiates acute liver failure from cases with acute severe liver injury: these latter cases usually survive spontaneously, but clinical models to predict the development of encephalopathy are poorly developed.

Epidemiology

As discussed above, a significant proportion of patients with acute liver failure have no specific cause identified using currently available diagnostic techniques i.e. indeterminate ALF. A number of centres, predominantly from the Western world, have reported the number of patients diagnosed with indeterminate ALF (Table 1 and Figure 4). In total; the studies included 5, 027 cases of acute liver failure, with 689 (~20%) incidents of indeterminate causation. There is some inherent heterogeneity between the studies including access to specialist referral units and particular serological tests; therefore the numbers should be interpreted with caution. It is well recognised that indeterminate acute liver failure is more common in the paediatric than adult population, however a detailed review of the paediatric literature is out with the scope of this review.

Potential Causative Factors of indeterminate hepatitis (Figure 3).

Parvovirus

Parvovirus B19 (PVB19) is commonly recognised as a self-limiting cause of acute hepatitis that usually has an indolent course and significant morbidity and mortality in paediatric patients. However, parvovirus is less common in the adult population. Huang[7] reported a case of active infection in an immunocompetent female patient. The infection was acquired from her child. The patient had significant transaminase elevation with coagulopathy and jaundice but no encephalopathy and went on to make an unremarkable recovery with supportive care. Ho[8] also described a case of parvovirus infection in an immunocompetent woman of Chinese origin who presented with significant transaminitis, jaundice and ascites. Liver biopsy was remarkable for scattered regenerative features but absence of fibrosis or lobular hepatitis. A bone marrow sample demonstrated large pro-erythrocytes containing nuclear inclusions and a paucity of mature erythroid precursors. Both IgM and IgG were positive for PVB19 infection, consistent with acute infection. In this case, infection was also self-limiting. In addition, Langnas[9] also proposed parvovirus B19 as a causative agent in a small case series of acute liver failure, all of which were associated with aplastic anaemia. Quite how parvovirus elicits a hepatotoxic effect is not completely understood but may relate to caspase 3-mediated apoptosis.[10] Adding parvovirus B19 IgM to an acute hepatitis screen may facilitate detection of unrecognised cases.

SEN Virus

SEN virus (SENV) is a relatively recently characterised, single-stranded DNA-virus of the Annelloviridae family and has been suggested as a potential causative agent of indeterminate hepatitis. The virus was named after the initials of the patient in whom it was first identified, who was also infected with human immunodeficiency virus. In 2013, Rizvi assessed the prevalence of SENV in cases of both acute and chronic hepatitis in an Indian population. [11] Within a population of 135 individuals with acute and chronic hepatitis they identified SENV in 34 individuals (25.2%). There were 3 patients with acute liver failure, all positive

for SENV-H genotype. In contrast, Umemura provided robust evidence against SENV being a potential cause of indeterminate acute liver failure demonstrating the presence of SENV in 8% of 99 cases of acute liver failure from the USA, whilst not a single incident case within the group of patients of liver failure due to indeterminate hepatitis was identified.[12]

More recently, further attempts to identify the presence of annelloviridae viruses in pathogenesis of indeterminate hepatitis have been undertaken using metagenomic techniques; however, once again there was no evidence to substantiate causality. [13]

Herpes simplex virus

Herpes simplex virus (HSV) hepatitis is an uncommon complication of HSV infection, which may result in acute liver failure. It represents less than 1% of all ALF cases and less than 2% of all viral causes of ALF[14] Acute HSV hepatitis is characterised by massive hepatocellular necrosis often without the well recognised mucocutaneous lesions. It is most prevalent in the immunosuppressed or during pregnancy, although one review proposed an incidence of ALF within an apparent immunocompetent cohort of 25% [15]. Levitsky [14] suggested that within a cohort of indeterminate hepatitis, 4 patients had evidence of acute HSV infection. Two of these individuals underwent emergency liver transplantation for ALF with concomitant antiviral therapy, despite this however 1 individual died. Both other acute liver failure patients died within 48 hours despite antiviral treatment.

Al-Midani[16] described two cases of acute liver failure secondary to HSV. Both these cases occurred in the context of immunosuppression post-renal transplantation. Both individuals were HSV-naïve and developed features of hyper-acute liver failure, with one of the patients dying of multiorgan failure and one surviving with aciclovir and immunoglobulin therapies. HSV serology should be performed and consideration given to empirical use of aciclovir before the results are available in patients with

indeterminate acute liver failure especially during pregnancy, early puerperium or in immunosuppressed patients [17].

Togavirus-Like Particles

Togavirus-like particles were previously detected in the native livers of almost 40% (n = 7) of patients transplanted for indeterminate hepatitis in a single UK centre.[18,19] These particles were not detected in the livers of patients transplanted for other causes of ALF, chronic liver disease or in healthy livers. Five patients with togavirus-like particles detected in their native liver developed early haemorrhagic hepatic failure post-transplant; the particles were again detected in all subsequent liver grafts, at a higher level than in the native liver.

Occult metabolic and genetic disorders

Occult metabolic and genetic disorders are more likely to be a factor in indeterminate acute liver failure in the paediatric population compared with the adult population. Urea cycle defects may cause acute liver failure in children; however, their possible causative role in adult indeterminate ALF is not well defined. It is important to consider these diagnoses, as rapid treatment may preclude the need for liver transplantation. These conditions are particularly important to consider in apparent 'repeated' indeterminate cases of severe acute liver injury or failure in young adults.

In a Caucasian cohort of patients with indeterminate hepatitis, a strong genetic preponderance was reported in individuals with the homozygous haplotype HLA A1-B8-DR3, conferring a relative risk of 9.7 times that of a control population of developing acute liver failure. The authors suggest that disordered MHC-restricted presentation of viral peptides and enhanced elimination of infected hepatocytes may underpin the pathogenesis. This genetic combination generally renders an individual C4 deplete, in addition to other aberrant innate immune coordination. Furthermore, homozygosity for this haplotype may be associated with non-specific perturbation of immune responses to a range of potentially

hepatotoxic agents (viral and others), and exceptional susceptibility to the development of lethal liver injury. [20]

Undetected paracetamol overdose

The measurement of paracetamol (acetaminophen) adducts in cases of indeterminate ALF has recently been the subject of debate and interest. Paracetamol – protein adducts are formed when NAPQI binds with the amino acid cysteine in cellular proteins after large dose paracetamol ingestion, and are released into the peripheral circulation as a consequence of hepatocyte necrosis, where they can then be detected. Khandelwal's study confirms and extends the previous reports[21] regarding the use of paracetamol - protein adduct measurement in the diagnostic evaluation of patients with acute liver failure. In this large data set using a refined assay method, paracetamol - protein adducts were detected in 95% of patients with clinically defined paracetamol overdose. In addition, nearly 19% of patients with acute liver failure classified as indeterminate had adducts detectable suggesting occult paracetamol toxicity not identified by experienced investigators using current diagnostic techniques.[22] However, these patients also had some clinical features and biochemical changes that might be suggestive of paracetamol overdose. A rapid, point of care test for paracetamol adducts has recently been developed by Roberts and colleagues[23] and will likely prove to be a valuable diagnostic adjunct in assessment of cases of indeterminate hepatitis where concerns persist of occult paracetamol ingestion. Detection of paracetamol overdose is important as a specific antidote is available, the clinical course is different and alternative criteria for transplantation are applied.

Haemophagocytic lymphohistiocytosis (HLH)

There have now been several case reports of haemophagocytic lymphohistiocytosis (HLH) causing acute liver failure, often being identified late in patients receiving an earlier diagnosis of indeterminate ALF.[24,25] HLH can be a primary or acquired disorder of uncontrolled immune regulation. HLH has a variable clinical

spectrum, but typically presents with high fever, hepatosplenomegaly, cytopaenia, coagulation abnormalities, histopathologic evidence of haemophagocytosis, and fatal multiple organ failure. [26] Liver injury is a common complication of HLH. Previous studies suggest that up to 85% of adult patients with secondary HLH have elevated transaminases and 50% have hyperbilirubinaemia. ALF is a rare presenting feature but often evolves with progression of multi-organ involvement. [27] Previously, HLH was considered a disease of childhood, however adult case series have begun to emerge, [28,29] with a single transplant centre[24] identifying 3 cases in an adult cohort in a single year. The true incidence in adults is unknown. Diagnostic criteria have been suggested for the paediatric population (Table 2).[30] These have not been validated in adult patients; however they may provide a diagnostic framework for consideration of potential cases.

Unrecognised idiosyncratic drug reactions and environmental toxins

Drug-induced liver injury (DILI) is a rare complication of many commonly prescribed drugs. It can therefore be difficult to ascertain whether a patient with DILI is in fact a patient with indeterminate acute liver failure who also happens to be taking a potentially hepatotoxic drug. Several causality scoring systems are described, but are rarely applied in clinical practice and an objective, reproducible clinical method of assessing drug=induced liver injury causality is still required [31]. There has been increasing interest in the recognition of DILI, with the establishment of a number of international corsortia specifically investigating this important topic, and as we learn more about DILI, more cases of apparent indeterminate hepatitis may in fact be attributed to DILI. A specific biomarker for DILI would allow clinicians to differentiate between unrecognised drug-induced liver injury and indeterminate acute liver failure, but has yet to be developed.

Environment and occupational agents and toxins have been proposed as a potential cause of indeterminate ALF. A high index of suspicion must be maintained to recognise an environmental or

occupational agent as the cause of ALF. Tetrachloroethylene has been reported to cause acute liver failure, with one patient recovering with steroids and plasmapheresis [32]. This presentation was similar to that of drug-induced liver injury, but in many patients history of exposure to this toxin may not be available. Several solvents are also implicated in causing acute liver injury, and again if exposure to these agents are not reported or identified, the patient may be mislabeled as having indeterminate ALF. These solvents include dimethylformamide, dimethylacetamide and trichloroethylene[33]. In a study of the latter, 10% of workers exposed to tricholoroethylene became jaundiced with massive hepatocyte necrosis[34]

Unrecognised or seronegative autoimmune disease

Undiagnosed autoimmune disease may contribute to the cause of 'indeterminate' acute liver failure. Some cases of apparent indeterminate ALF occur in young females with history of other autoimmune disease and suggestive features of autoimmune hepatitis on histological analysis. The American Acute Liver Failure Study Group (ALFSG) investigated 72 patients with a diagnosis of indeterminate hepatitis who had a biopsy or explant available for review. The reviewing pathologist was blinded to all clinical information, and diagnosed autoimmune liver disease on the basis of histological findings in 58% of patients. However, 50% of these had detectable anti-nuclear antibody (ANA) (titre not reported), 63% detectable ANA+/-ASMA and mean ALT 1134 IU/L[35]. In a population of predominantly young Caucasian females, these clinical features alone may have pointed towards a potential diagnosis of AIH.

In a cohort of 73 acute liver failure patients of varying aetiologies, Bernal demonstrated the presence of features of autoimmunity, including antibodies to soluble liver antigen (Anti-SLA) and other non-organ specific antibodies (NOSA). Autoantibodies were absent in paracetamol-related cases and present in 23 of 53 of non-paracetamol cases; anti-SLA (n=16), ANA (6), ASM (4) and AMA (1). There were 16 cryptogenic cases; 5 of whom had anti-SLA. AIH scores classified 50% of cryptogenic cases as "probable autoimmune hepatitis". [36]

Re-evaluation of aetiology

The American Liver Failure Study Group (ALFSG) recently re-evaluated 314 cases of patients who had previously been given a diagnosis of indeterminate ALF [37]. Patient samples were retrospectively tested for paracetamol adducts, occult viral sequences by microarray analysis and deep sequencing; if available, liver histology was also re-reviewed. As a result of these further tests, 49% of patients (49% of 294 with complete information) received a new diagnosis; of these, 43 patients were diagnosed as acute liver failure due to paracetamol overdose, 33 autoimmune hepatitis, 7 viral cases (1 PVB19, HBV, EBV, VZV and 3 HSV), and 23 drug-induced liver injury using the DILI network model. In those patients in whom an alternative diagnosis was not made, the diagnosis was 'indeterminable' if key diagnostic information was missing, and 'truly indeterminate' if complete diagnostic information was available. 31% were defined as truly indeterminate, making up just 3.3.% of acute liver failure cases in the ALFSG registry overall. This figure is lower than that reported in other studies, suggesting that diagnostic techniques as described above do need to be more widely adopted to ensure a correct diagnosis is made.

Clinical features

Indeterminate hepatitis usually results in subacute liver failure, with the symptoms typically present greater than 4 weeks before the development of encephalopathy. There is a female preponderance reported in all cases series, with a bimodal age distribution. Table 1 records the percentages of patients with indeterminate liver failure contributing to reported cohorts of patients with ALF. The highest reported percentage of patients with indeterminate acute liver failure was reported in Sudan[13], however their access to certain diagnostic techniques may be limited. A group from China also reported a higher percentage of patients with indeterminate acute liver failure compared with other studies[20], however it must be borne in mind that this study included paediatric patients.

Prodromal symptoms are non-specific, including fatigue, myalgia and nausea. Often these symptoms can be mistaken for a viral prodrome. Biochemically, these patients demonstrate lower transaminases and higher bilirubin levels, similar to other causes of subacute ALF and in contrast with the high transaminases and lower bilirubin levels seen in hyperacute liver failure, especially paracetamol toxicity. Other clinical features include a lesser degree of coagulopathy, and less renal failure and acidosis when compared with paracetamol toxicity.

The American Liver Failure Study Group have previously described the demographics of patients registered with indeterminate hepatitis on the ALFSG Adult Registry between 1998 and 2014[38]. The main findings are summarised in Table 3. In a separate cohort of 140 patients with indeterminate (seronegative) acute liver failure, Wigg observed similar clinical features: 59% of the cohort were female. Of those proceeding to transplantation, the mean age was 40 years, and 86% were Caucasian. 49% had grade 3-4 hepatic encephalopathy prior to transplantation[39].

Association with aplastic anaemia

Indeterminate hepatitis is the most common cause of ALF with associated aplastic anaemia[40]. The presence of aplastic anaemia increases the mortality associated with acute liver failure and may not resolve following transplantation, necessitating post-transplant treatment with immunosuppressive therapy or even haematopoietic cell transplantation. The presence of aplastic anaemia raises the suspicion that a viral aetiology is the cause for indeterminate disease [9].

Management

The principle goal of management of acute liver failure (regardless of aetiology) is to achieve metabolic and haemodynamic stability to provide optimal conditions for hepatic regeneration and minimisation of associated complications. Early identification of individuals with a significantly reduced chance of

spontaneous survival enhances the provision of successful emergency liver transplantation. The treatment is generally founded on the basic principles applied to other critically unwell patients, with some specific caveats. [41]

Medical management

Some aetiologies of acute-liver failure have a specific treatment or antidote available. Unfortunately, this is not the case for indeterminate hepatitis. Management is therefore supportive, and several guidelines are available to advise the general and critical care management of these patients. The main aspects of organ specific supportive management as recommended by EASL and AASLD are compared in Table 4.

- *N-acetylcysteine (N-Ac)*

NAC has complex antioxidant and immunological effects that may benefit individuals with non-paracetamol-related acute liver failure. Stravitz[42] demonstrated that interleukin-17 was an independent predictor of poor outcome in patients with non-paracetamol ALF; higher interleukin-17 levels were associated with progression of hepatic encephalopathy and decreased with NAC administration. However, this survival benefit of N-Ac seems to be limited to those non-paracetamol patients with Grade I-II encephalopathy.[43] More recently Darweesh[44] demonstrated a greater degree of spontaneous recovery in NAC treated patients, particularly those with coagulopathy only. A reduction in the development of encephalopathy during admission (33% vs 63%; p = 0.02) was observed. However, this cohort did not include any individuals with indeterminate liver failure as a diagnosis and consisted principally of viral hepatidities, drug-induced variants and pregnancy-related complications. It is therefore difficult to derive any significance in the case of indeterminate aetiologies, but many centres will utilise N-Ac in cases of indeterminate hepatitis.

A multi-centre prospective double-blind trial of NAC in patients with non-paracetamol ALF was undertaken by the Acute Liver Failure Study Group (ALFSG) [45]. The treatment group received NAC via

infusion for 72 hours. There was no difference in overall survival at 3 weeks in those patients receiving N-Ac versus placebo. However, transplant free survival was significantly improved in those patients receiving NAC, but this benefit was largely confined to those patients with a low coma grade (transplant free survival in patients with coma grade I-II; 52% in N-Ac group versus 30% in placebo group). The authors therefore cautiously advised that N-Ac be considered for early non-paracetamol ALF but that its use must not delay referral to a transplant centre.

- *Corticosteroids*

The use of corticosteroid therapy in acute liver failure has been controversial. A study by Karkhanis[46] suggested that corticosteroids did not improve overall survival or spontaneous survival in drug-induced, indeterminate, or autoimmune ALF and were associated with lower survival in patients with the highest MELD scores. More recently, a retrospective analysis reviewed the survival in individuals with both acute and subacute liver failure in Chongqing, China. They confirmed previous findings whereby those individuals with high grade encephalopathy or Model for End-stage Liver Disease (MELD) scores greater than 35 did particularly poorly. Nevertheless, they did suggest improved rates of spontaneous survival associated with steroid use among patients who had significantly elevated alanine aminotransferase (ALT) greater than 30 x the upper limit of normal and coma grade less than 4 with MELD scores less than 35. This finding was most significant in those with an illness duration of less than 2 weeks. [47] Unfortunately they did not specify outcomes for different aetiologies and it is therefore hard to evaluate any specific benefit in indeterminate hepatitis. Given the relative lack of robust evidence in indeterminate liver failure, steroid therapy cannot be advocated unless there is significant concern regarding underlying autoantibody negative autoimmune hepatitis.

Prognostication and emergency liver transplantation

The early identification of individuals with acute liver failure and significantly reduced spontaneous survival with medical therapy is crucial in identifying candidates for emergency liver transplantation. In patients with indeterminate hepatitis on the ALFSG Adult Registry between 1998 and 2013, 57% of patients with indeterminate hepatitis were listed for transplant, with a transplant free survival rate of 27.5% [48]. In the remainder of the western world, the spontaneous (transplant free) survival rate for indeterminate liver failure is also quoted between 20-25%, in comparison with 65% spontaneous survival in patients with paracetamol induced acute liver failure[49].

Various prognostic criteria are applied throughout the world. Common features of these models include age and increased severity of liver failure defined by the degree of coagulopathy and jaundice. [41]The Kings College Criteria have traditionally been used in the UK and elsewhere in the western world to predict poor outcome. In patients with a non-paracetamol aetiology such as indeterminate hepatitis, an INR > 6.5 and three or more of the following were predictors of a poor outcome: unfavourable cause (not hepatitis A or B viral infection), jaundice to encephalopathy time greater than 7 days, age less than 10 or more than 40 years, INR more than 3.5 and bilirubin more than 300umol/L. In many studies including systematic reviews and meta-analyses, these criteria have consistently demonstrated high specificity but lower sensitivity and negative predictive value[50]. In the UK, the criteria used to list patients for emergency liver transplantation have recently been modified [51]. These refined criteria recognise the importance in distinction between favourable and unfavourable aetiology in prognosis in the sub-group of patients with non-paracetamol aetiologies, with indeterminate hepatitis being considered unfavourable. The new criteria now allow emergency liver transplant listing of a patient with indeterminate hepatitis in the absence of hepatic encephalopathy, recognising that this sign is often a very late development in the clinical course of these patients and by the time hepatic encephalopathy has developed the patient may be too sick to survive transplant (particularly if encephalopathy has been precipitated by infection). The current UK listing criteria are shown in Table 5.

In 2012, Wlodzimirow performed a systematic review of newly developed and modified existing prognostic models of mortality for acute liver failure [52]. This review ultimately identified that although many studies describing new models are available, these studies demonstrate methodological and reporting limitations, and are not yet suitable for general clinical application. The Model for End Stage Liver Disease (MELD) score has been proposed as an alternative to the Kings College Criteria. A recent meta-analysis quantitatively assessed and compared their prognostic accuracy in acute liver failure. In non-paracetamol causes, the Kings College Criteria demonstrated a sensitivity of 58%, specificity of 74% and diagnostic odds ratio of 4.16; MELD demonstrated a sensitivity of 76%, specificity of 73% and diagnostic odds ratio of 8.42. This study suggested the MELD may be a better predictor of mortality in patients with non-paracetamol acute liver failure. However, studies were limited by multiple factors such as small sample sizes, disease heterogeneity and classification (or not) of transplanted patients as non-survivors. The Acute Liver Failure Study Group recently published a model to predict 21-day transplant free survival (not death, the outcome of interest in most prognostic models) in patients with acute liver failure. [53] The aetiology of liver injury is a key component of this model, with indeterminate hepatitis again considered as an unfavourable aetiology. This model was highly specific but had much reduced sensitivity (specificity 95.3%, sensitivity 37.1%, AUC 0.84) in predicting 21-day spontaneous survival, and requires validation in external cohorts.

Emergency Liver Transplantation

Patients with indeterminate acute liver failure have a reduced spontaneous survival compared with other aetiologies. The lack of specific medical therapy results in emergency liver transplantation forming the mainstay of treatment in severe cases. Emergency transplantation has resulted in significant improvement in survival in patients with indeterminate acute liver failure over several decades [54]. Most countries operate an organ allocation system that offers patients with acute liver failure the highest priority; most cases being transplanted within 48 hours of listing. In contrast with paracetamol induced liver failure, the

mortality on the waiting list is reduced in cases of indeterminate ALF. The ALFSG recently reported 21 day outcomes in patients who were listed for urgent transplantation for a variety of aetiologies. 114 patients were listed for indeterminate ALF; 84 (73.6%) proceeded to transplantation, 15 (13.2) died and 15 (13.2%) spontaneously survived. These outcomes were significantly different to those reported for patients with paracetamol induced acute liver failure; in this cohort, 35.8% (n = 62) proceeded to liver transplantation, 41 (23.7%) died and 70 (40.5%) spontaneously survived, highlighting the important role emergency transplantation has in the management of indeterminate acute liver failure.

Bernal reported that use of transplantation for non-paracetamol liver failure has increased over time, with the proportion of patients undergoing transplantation being higher in non-paracetamol cases compared with paracetamol cases[54]. Survival following transplantation has also increased over time, likely as a result of improvements in surgical, medical and intensive care management. However, in the same cohort, no improvement in transplant free survival was noted over time. Donnelly also recently reported an increase in survival post transplantation for patients with non-paracetamol acute liver failure, with a trend towards improvement in transplant free survival also observed [49]. There is no doubt that transplantation is the only rescue therapy proven to be of benefit in selected patients with severe indeterminate hepatitis, and other treatment options are desperately needed so as not to disadvantage those on the elective liver transplant waiting list.

Future therapies and strategies

Future work and research should focus on developing large international registries of patients with indeterminate acute liver failure, which may help to identify population based factors associated with the development of the disease, which in turn may point towards a specific aetiological agent or trigger. Such registries may also identify common clinical features allowing earlier diagnosis and prognostication.

"Omic" technologies will likely have a role to play in the future in both the diagnosis and prognosis of indeterminate acute liver failure. Metabolomics studies a set of metabolites present in biological fluids, and facilitates the discovery of specific metabolic profiles associated with a disease. However, this is a technique still early in clinical application and it is unlikely to be used extensively in the near future. Sequencing and microarray technology may allow the detection of novel viruses. Such technology has already been successful in identifying a virus associated with prostate cancer and novel viral causes of SARS [55]. Although potential viral causes may be identified this way, demonstrating a true causal relationship will be challenging. Whole exome sequencing has been used in the paediatric population to identify rare causes of ALF in patients who were otherwise labelled as having an indeterminate cause. Causes of ALF identified using this technique include mitochondrial disorders and syndromic cholestasis due to *NOTCH2* mutations [56]. Recently, Somasekar used metagenomic next-generation sequencing (mNGS) with confirmatory Nucleic Acid Testing (NATs) in a cohort of 178 patients with indeterminate hepatitis. Within this group they identified eight cases of previously unrecognised viral infections. These included 4 cases of HSV-1 (with one hepatitis B (HBV) co-infection), in addition to single instances of hepatitis B virus, parvovirus B19, human herpes virus-7 (HHV-7) and cytomegalovirus. [57]

Conclusions

The 'indeterminate' aetiology is a relatively common cause of acute liver failure in the western world. Potential unrecognised causes of this clinical condition include viral agents which are undetected via routine screening, missed paracetamol overdose or other drug induced liver injury, and seronegative autoimmune disease. It is likely that there is no single causative factor. Medical management is supportive, but indeterminate hepatitis has a poor overall outcome with transplantation being the only curative option available at present. Further research in this field is desperately required, to identify any

aetiological agents, develop specific therapy and to reduce the number of patients who require emergency liver transplantation.

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(iii) All authors approve the final manuscript

Statement of Interests

The authors declare no conflicts of interest relating to this work.

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Tables

Table 1**:** Cohort studies of Acute Liver Failure (ALF) with incidence of indeterminate hepatitis reported

ADULT STUDY	*COHORT (Country)*	*PERCENTAGE OF PATIENTS WITH INDETERMINATE ALF*
Ostapowicz G et al[58]	308 adult patients with ALF (*US*)	17%
Wigg et al[39]	Adult patients with ALF (*United Kingdom*)	16%
Mudawi HM et al[59]	37 patients with ALF (*Sudan*)	38%
Areia M et al[60]	61 cases of ALF (*Portugal*)	26%
Adukauskiene D et al[61]	28 adult patients with ALF (*Lithuania*)	17.9%
Canbay A et al[62]	134 adult patients with ALF 2002-8 (*Germany*)	20.9%
Marudanayagam R et al[63]	1,237 adult patients with ALF (*United Kingdom*)	15%
Coilly A et al[64]	541 adults patients with ALF (*France*)	13%
Hadem J et al[65]	155 adult patients with severe ALI and ALF (*Germany*)	24%
Zhao P et al[66]	177 patients aged > 12 years with ALF (*China*)	29.38%
Fabrega E et al[67]	17 adults patients with ALF (*Spain*)	24%
Fujiwara K et al[68] *)*	106 adult patients with ALI or ALF (*Japan*)	22.6%
Reddy KR et al[69]	614 adult patients with ALF (*United States*)	18.6%
Donnelly MC et al[49]	1,164 adult patients with ALI and ALF (*Scotland*)	5.5%

Table 2. Diagnostic criteria for Haemophagocytic Lymphohistiocytosis (HLH) (adapted from Diagnostic and Therapeutic Guidelines for Haemophagocytic Lymphohistiocytosis; *Pediat. Blood Cancer* 2007)

The Diagnosis of HLH may be established by 1. *A molecular diagnosis consistent with HLH* *(e.g. Mutations associated with PRF1, UNC13D, STX11)* *Or*
2. *Presence of 5 of 8 of the following:* a. *Fever (>38.5^{o} for 7 days)* b. *Splenomegaly* c. *Cytopaenias (Affecting at least 2 of the 3 following lineages in peripheral blood)* 1. *Haemoglobin (<9g/dL)* 2. *Thrombocytopaenia (<100x10^{9}/L)* 3. *Neutropaenia (<1x10^{9}/L)* d. *Hypertriglyceridaemia (fasting >2mol/L) and/or hypofibrinogenaemia (<1.5g/l)* e. *Haemophagocytosis (Bone Marrow, Spleen or Lymph Nodes)* f. *Low or Absent NK activity* g. *Ferritin >500µg/ml* h. *Soluble CD25 >2400U/ml*

Table 3: Demographics within cohort of indeterminate hepatitis (unpublished data- American Liver Failure Study Group (ALFSG)[38] and Scottish Liver Transplantation Unit (SLTU))

Demographics:	*USALF (n=245, 1998-2014)*	*SLTU (n=105; 1992-2017)*
Age (Years)	39	45 [34 - 57]
Sex (% Female)	59	70.5%
Jaundice to coma (Days)	11	
HE grade >3 (%)	48	
ALT (IU)	865	972 [390 - 2095]
Bilirubin (µmol/l)	361	406 [148 - 515]
Creatinine (µmol/l)		67 [90 - 176]
Prothrombin Time (sec)		22 [32 - 45]

(Continuous data are median and IQR)

Table 4**:** Comparison of European Association for Study of the Liver (EASL) vs American Association for Study of Liver Disease (AASLD) statements on management of acute liver failure (ALF)

	European Association for Study of the Liver (EASL) Recommendations [70]	**American Association for the Study of Liver Disease (AASLD) Recommendations** [71]
Cardiovascular	1. Resuscitation with crystalloid (evidence level II-1; GR = 1) 2. Persistent hypotension necessitates critical care management with vasoactive agents as guided by monitoring (evidence level II-3, GR=1) 3. Norepinephrine is preferable vasopressor (evidence level III, GR = 1) 4. A blood pressure target has not been defined in the literature (evidence level III, GR=2) 5. Hydrocortisone therapy does not reduce mortality but does decrease vasopressor requirements (evidence level II-1, GR = 1)	1. Fluid resuscitation and maintenance of adequate intravascular volume are recommended on presentation in patients with ALF. The initial treatment of hypotension should be with intravenous normal saline (III). 2. Systemic vasopressor support with agents such as norepinephrine should be administered in volume-refractory hypotension or to ensure adequate CPP. Vasopressin or terlipressin can be added to norepinephrine in norepinephrine-refractory cases, but should be used cautiously in severely encephalopathic patients with intracranial hypertension (II-1) 3. Goals of circulatory support in patients with ALF are a MAP ≥75 mmHg and CPP 60-80 mmHg (II)
Respiratory	1. Standard sedation and lung protective ventilator techniques should be utilised in patients with ALF (evidence level II-3, GR = 1) 2. Avoid of excessive hyper or hypocarbia (evidence level III, GR =1) 3. Regular chest physiotherapy should be carried out and ventilator associated pneumonia (VAP) avoided (evidence level III, GR =1)	1. Not specified
Renal	1. Early institution of renal replacement therapy (RRT) should be considered for persistent hyperammonaemia, control of hyponatraemia and other metabolic derangements, fluid balance and temperature regulation (evidence level III, GR=1) 2. Anticoagulation of RRT is ambiguous and if citrate is utilised should mandate close monitoring of metabolic state (evidence level II-2, GR=1) 3. Continuous RRT is preferable to intermittent haemodialysis (evidence level III, GR=1)	1. If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used (I).
Gastrointestinal	1. Patients with ALF should be considered for enteral or parenteral nutrition (evidence level II-3, GR=1) 2. Avoid NG feeding in patients with progressive encephalopathy (evidence level III, GR=1) 3. PPI administration should be balanced against the risk of VAP and clostridium Difficile infection (evidence level Ii-3, GR=1)	1. Patients with ALF in the ICU should receive prophylaxis with H2 blocking agents or proton pump inhibitors (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (I)
Biochemical/Metabolic considerations	1. Stringent attention to normalisation of biochemical abnormalities is warranted in ALF (evidence level III, GR=1) 2. Hypoglycaemia is common in patients with ALD and associated with increased mortality (evidence level II-3, GR=1)	1. Metabolic homeostasis must be carefully maintained in ALF patients. Overall nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently, with expeditious correction of derangements (III)

	3. Hyponatraemia is detrimental to outcome and should be corrected to maintain concentrations of 140-150mmol/l (evidence level II-2, GR=1) 4. Lactate elevation is related to increased production and reduced clearance and remains a poor prognostic marker. RRT is indicated to correct acidosis and metabolic disturbances (evidence level II-3, GR=1)	
Infection/SIRS	1. Prophylactic antibiotics, non-absorbable antibiotics and antifungal therapy has not been shown to improve survival in ALF (evidence level II-2, GR=1) 2. Early anti-infection treatments should be introduced upon appearance of progression of hepatic encephalopathy, clinical signs of infections, or elements of SIRS (evidence level II-3, GR=1) 3. Antifungal therapy in those with prolonged critical care support for multiple organ failure should be considered, as guided by the use of biomarkers (evidence level II-3, GR=1)	1. Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy (III) 2. Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS) (III)
Neurological	1. Patients with low grade encephalopathy should be frequently evaluated for signs of deterioration (evidence level III, GR=1) 2. Patients with Grade 3 or 4 encephalopathy , intubation should be undertaken. Regular evaluation for signs of intracranial hypertension should be performed (evidence level III, GR=1) 3. Trans-cranial doppler is a useful non-invasive monitoring tool (evidence level II-3, GR=1) 4. Invasive intracranial pressure monitoring should be considered in a highly selected subgroup of patients, who have progressed to grade 3 or 4 coma, are intubated and ventilated and deemed at high risk of Intracranial hypertension (ICH) (evidence level II-3, GR=1) 5. Mannitol or hypertonic saline should be administered for surges of ICP with consideration for short-term hyperventilation. Mild hypothermia and indomethacin may be considered in uncontrolled ICH (evidence level II-2, GR=1)	1. In the absence of ICP monitoring, frequent (hourly) neurological evaluation is recommended to identify early evidence of intracranial hypertension (III) 2. Intracranial pressure monitoring is recommended in ALF patients with high grade hepatic encephalopathy, in centers with expertise in ICP monitoring, in patients awaiting and undergoing liver transplantation (III) 3. Patients who progress to high-grade hepatic encephalopathy (grade III or IV) should undergo endotracheal intubation (III) 4. In the event of intracranial hypertension, a mannitol bolus (0.5-1.0 gm/kg body weight) is recommended as first-line therapy; however, the prophylactic administration of mannitol is not recommended (II-2) 5. In ALF patients at highest risk for cerebral edema (serum ammonia >150 µM, grade 3/4 hepatic encephalopathy, acute renal failure, requiring vasopressors to maintain MAP), the prophylactic induction of hypernatremia with hypertonic saline to a sodium level of 145-155 mEq/L is recommended (I)

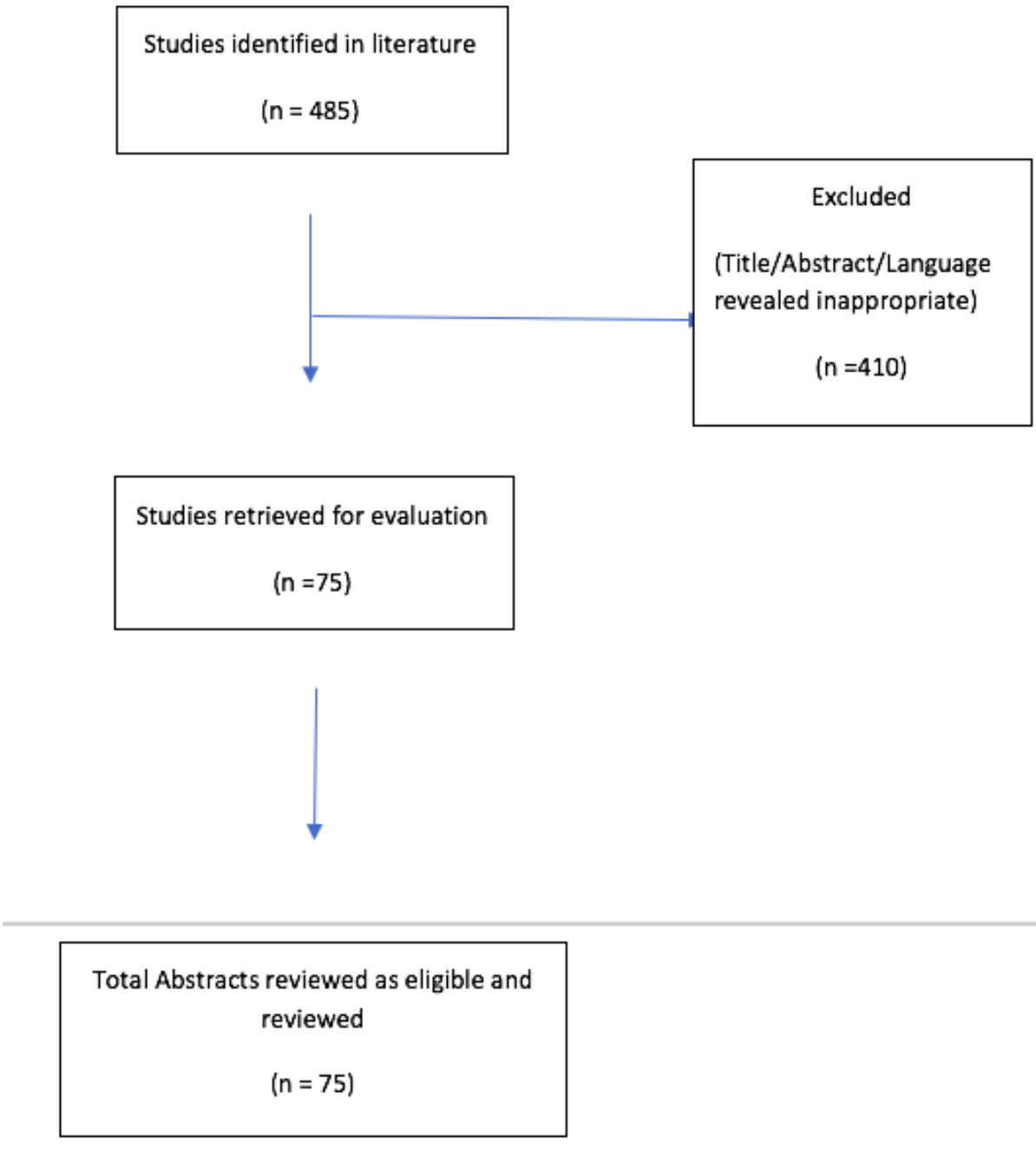
Legend; ALD- Alcoholic Liver Disease, ALF- Acute Liver Failure, CPP- Central Pulse Pressure, MAP – Mean Arterial Pressure, NG- Nasogastric, PPI- Proton Pump Inhibitor, SIRS- Systemic Inflammatory Response Syndrome, RRT- Renal Replacement Therapy

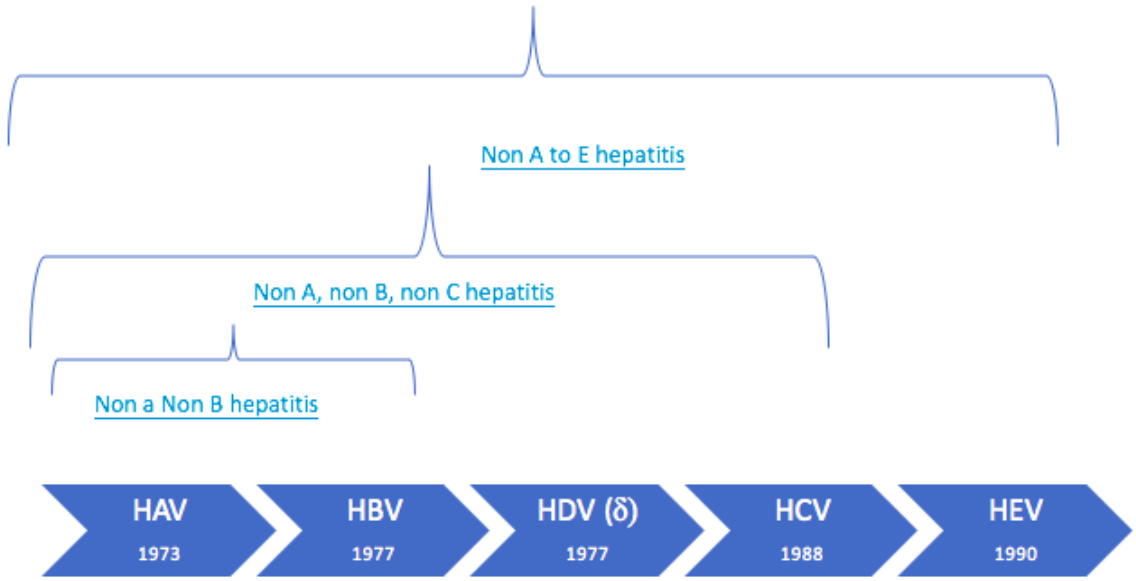
Table 5: Current UK listing criteria for super-urgent liver transplantation

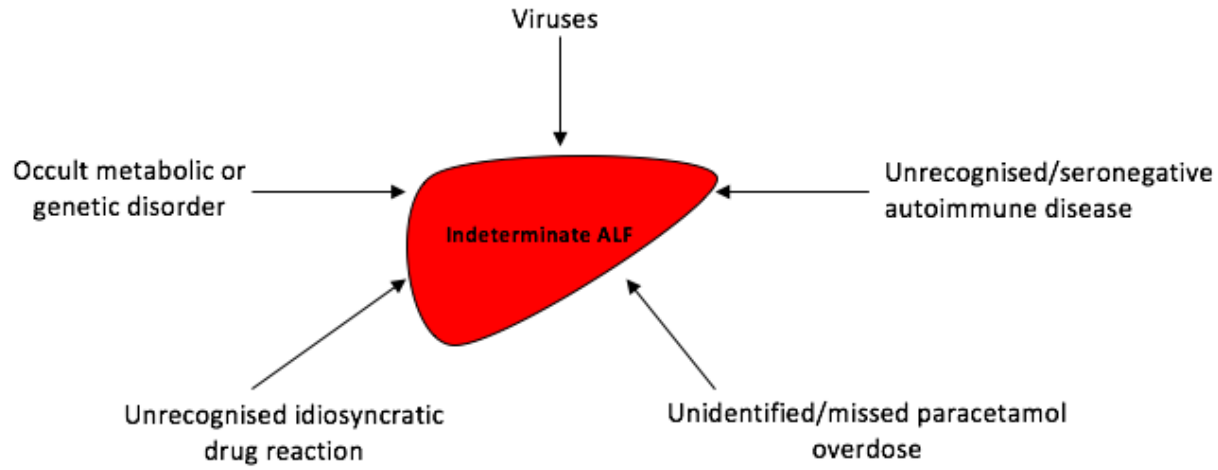
	AETIOLOGY	CRITERIA
CATEGORY 1	Paracetamol	pH < 7.25 more than 24 hours after overdose and after fluid resuscitation
CATEGORY 2	Paracetamol	Co-existing prothrombin time >100 seconds or INR >6.5, and serum creatinine >300 umol/L or anuria, and grade 3-4 encephalopathy
CATEGORY 3	Paracetamol	Significant liver injury and coagulopathy following exclusion of other causes of hyperlactataemia after adequate fluid resuscitation: arterial lactate >5mmol/L on admission and >4mmol/L 24 hours later in the presence of clinical hepatic encephalopthy
CATEGORY 4	Paracetamol	Two of the three criteria from Category 2 with clinical evidence of deterioration (eg increased ICP, FiO2 >50%, increasing inotrope requirements) in the absence of clinical sepsis
CATEGORY 5	Favourable non-paracetamol (such as acute viral hepatitis or ecstasy/cocaine induced ALF)	The presence of clinical hepatic encephalopathy is mandatory and: prothrombin time >100 seconds, or INR >6.5, or any three from the following: age <10 or >40 years, prothrombin time > 50 seconds or INR > 3.5, any grade of hepatic encephalopathy with jaundice to encephalopathy time > 7 days, serum bilirubin > 300umol/L
CATEGORY 6	Unfavourable non-paracetamol (such as seronegative hepatitis or idiosyncratic drug reactions)	a) Prothrombin time > 100 seconds or INR > 6.5 b) In the absence of clinical hepatic encephalopathy then INR >2 after vitamin K repletion is mandatory and any two from the following: age <10 or > 40 years, prothrombin time >50 seconds or INR > 3.5; serum bilirubin > 300 umol/L and if encephalopathy is present then jaundice to encephalopathy time > 7 days.
CATEGORY 7	Acute presentation of Wilson disease or Budd-Chiari syndrome	A combination of coagulopathy and any grade of encephalopathy

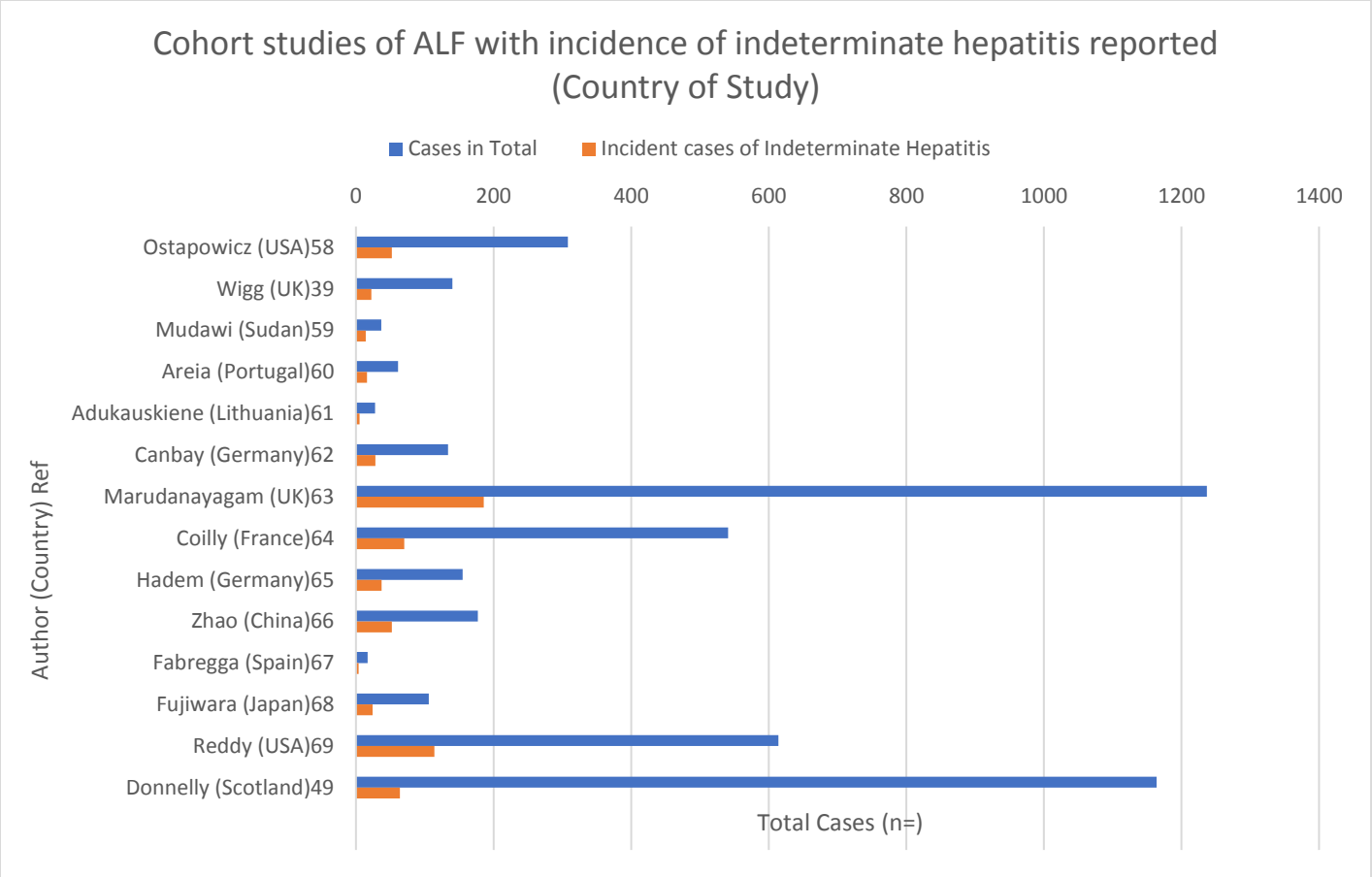
Legend: ICP- Intracranial Pressure, INR- International Normalised Ratio

Figures


Studies identified in literature
(n = 485)
Excluded
(Title/Abstract/Language revealed inappropriate)
(n =410)
Studies retrieved for evaluation
(n =75)
Total Abstracts reviewed as eligible and reviewed
(n = 75)


Non A to E hepatitis
Non A, non B, non C hepatitis
Non a Non B hepatitis
HAV
1973
HBV
1977
HDV (δ)
1977
HCV
1988
HEV
1990


Viruses
Occult metabolic or genetic disorder
Unrecognised/seronegative autoimmune disease
Indeterminate ALF
Unrecognised idiosyncratic drug reaction
Unidentified/missed paracetamol overdose


Cohort studies of ALF with incidence of indeterminate hepatitis reported (Country of Study)
Cases in Total
Incident cases of Indeterminate Hepatitis
0
200
400
600
800
1000
1200
1400
Ostapowicz (USA)58
Wigg (UK)39
Mudawi (Sudan)59
Areia (Portugal)60
Adukauskiene (Lithuania)61
Canbay (Germany)62
Marudanayagam (UK)63
Coilly (France)64
Hadem (Germany)65
Zhao (China)66
Fabregga (Spain)67
Fujiwara (Japan)68
Reddy (USA)69
Donnelly (Scotland)49
Author (Country) Ref
Total Cases (n=)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2, 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2, 5, 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, 34
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	34
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	26,28
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Throughout Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Throughout Discussion

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19, 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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